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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/423,035	01/13/2000	GERALD F. JOYCE	TSRI463.4	6257

7590 03/04/2005

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 03/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/423,035	JOYCE ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-29 and 31-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *29,31-36,38-42 and 47-49* is/are allowed.

6)☒ Claim(s) *1,10,18,19,25-28,37,43-46 and 50* is/are rejected.

7)☒ Claim(s) *3-9,11-17 and 20-24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/7/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

The restriction requirement between SEQ ID NOS: 102-119 originally made February 10, 2004 is withdrawn. Additionally, the examiner has rejoined claims 23 and 24, withdrawn in response to an election without traverse on January 10, 2002.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cleavage of a substrate by introduction of catalytic DNA into a cell in vitro, does not reasonably provide enablement for cleavage of a substrate by introduction of catalytic DNA into a cell where the cell is in an organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

1. The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the

art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

2. Claims 28 is directed to a method of cleaving a target nucleic acid in a cell using a catalytic DNA defined by claim 1. Claims 25-27 embrace the scope of claim 28. These claims encompass embodiments wherein the cell is located in cell culture as well as embodiments where the cell is in an organism and where the method may be performed for therapeutic purposes.

3. The specification teaches enzymatic DNA molecules capable of cleaving a substrate and on pages 25 and 26 contemplates their use in therapeutic applications. The specification contains examples of substrate cleavage under simulated physiological conditions. There are no examples in the specification describing use of catalytic DNA in any cells, either in culture or in an organism and no examples describing therapeutic use of catalytic DNAs.

4. The state of the art prior art is such that using nucleic acids for many applications *in vitro* is routine, but *in vivo* use of nucleic acids for any application, including therapeutic use, at the time of filing and even to the present time is not routine for several reasons, including the problems of delivery, specificity and duration.

5. The problems of nucleic acid based therapies are well known in the art, particularly with regard to the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect. For example, at the time the instant invention was made, the therapeutic use of nucleic acids was a highly unpredictable art due to

obstacles that continue to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, 2000, vol 6, p 72-81), Opalinska et al. (Nature Reviews Drug Discovery, 2002, vol 1, p. 503-514) Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonspecific effects.

6. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

7. Opalinska et al. state on page 511, "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and in column 2 of the same page, "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal

and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

8. Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in an organism. The specification provides examples of substrate cleavage by catalytic DNAs under simulated physiological conditions, however, such examples would not be predictive of *in vivo* activity and do not provide guidance on how to deliver oligonucleotides to any organism. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see p 79-80, section entitled "Cellular uptake facilitators for *in vitro* studies") states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....*In vitro*, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

9. Given these teachings, the skilled artisan would not know *a priori* whether introduction of catalytic DNAs *in vivo* would result in the oligonucleotide reaching the proper cell in a sufficient concentration and remaining for a sufficient time to cleave a target gene. One of skill in the art would not know how to deliver oligonucleotides to an

organism in such a way that would ensure an amount sufficient to cleave a target gene and have a therapeutic effect is delivered to the proper cell.

10. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically. The specification does not provide the guidance required to overcome the art-recognized unpredictability of using oligonucleotides in therapeutic applications in any organism. The field of nucleic acid therapeutics does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods.

11. Thus, while the specification is enabling for cleavage of a substrate in vitro or in a cell in culture, the specification is not enabling for the broad claims of cleaving a target gene in any organism as the art of introducing oligonucleotides into an organism is neither routine nor predictable. In order to practice the claimed invention in vivo in all organisms a number of variables would have to be optimized, including 1). the mode of delivery of the antisense oligonucleotide to an organism that would allow it to reach the targeted cell, 2). the amount of catalytic DNA that would need to be delivered in order to cleave the target once it reached the proper cell and 3). ensuring the catalytic DNA remains viable in a cell for a period of time that allows cleavage of the target to an extent that there is a measurable and significant therapeutic effect. Each one of these variables would have to be empirically determined for each catalytic DNA. While optimization of any single one of these steps may be routine, when taken together the amount of experimentation required becomes such that one of skill in the art could not

practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claim 28 is not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 10 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 10 is directed to a catalytic DNA with a core structure that comprises "a phosphorothioate nucleoside residue on a dipyrimidine". Claim 37 recites the same limitation in a method of engineering a catalytic DNA. The metes and bounds of this claim are unclear because "a...residue" indicates the singular case while the use of dipyrimidine indicates more than one residue. Is this claim meant to refer to two pyrimidines separated by a phosphorothioate internucleoside linkage?

13. Claims 43, 45 and 50 recite the limitation "said endonuclease activity". There is insufficient antecedent basis for this limitation in the claim. Claims 44 and 46 are rejected for the same reasons as they depend from claims 43 and 45, respectively.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11

F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1, 18 and 19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22 and 23 of U.S. Patent No. 6,326,174. Claims 25-27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 67 of U.S. Patent No. 6,326,174. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '174 patent are encompassed by the instant claims. Claim 1 of the instant application is directed to a catalytic DNA molecule having endonuclease activity that has a core structure shown as formula II. Claims 18 and 19 limit claim 1 by stating the activity of the catalytic DNA is enhanced by divalent cations, particularly Mg2+. Claims 22 and 23 of the '174 patent are directed to catalytic DNA molecules identified by SEQ ID NOS: 52-101 that have enhance activity in the

presence of Mg2+. Of the sequences recited in claim 22, SEQ ID NOS: 81 and 85-87 (and possibly others) share a common catalytic core that is identical to formula II, making the claims of the '174 patent a species of the generic claims of the instant application.

15. Claims 25-27 of the instant application are directed to a method of cleaving a target nucleic acid using a catalytic DNA having a structure defined by claim 1. Claim 67 of the '174 patent is directed to a method of cleaving a phosphoester bond by mixing a catalytic DNA with a substrate, making the claim of the '174 patent one embodiment of the broader instant claim.

Allowable Subject Matter

16. Claims 29, 31-36, 38-42 and 47-49 are allowed.

17. Claims 3-9, 11-17 and 20-24 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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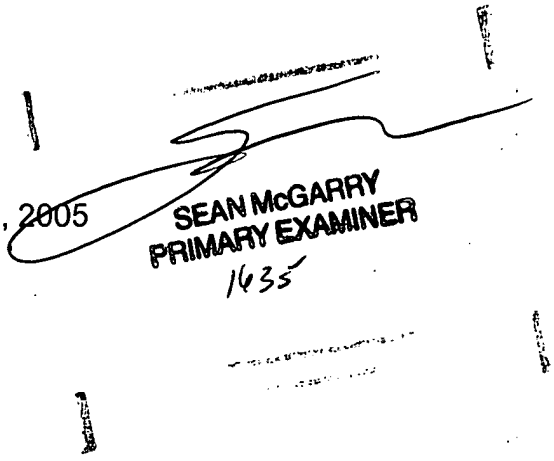

Tracy Vivlemore
Examiner
Art Unit 1635

TV
February 18, 2005